Remarks

The Office Action mailed January 11, 2002 has been received and reviewed. Claims 1-7 and 16-19 having been cancelled without prejudice, claims 9, 28-30, 33, 36-38 having been amended, and claims 41 and 42 having been added, the pending claims are claims 9-15 and 20-42. Reconsideration and withdrawal of the rejections are respectfully requested.

The amendment to claim 9 is supported by the specification at, for instance, page 14, lines 6-28.

Claim 28 is supported by the specification at, for instance, page 16, line 26 through page 17, line 4.

Claim 29 is supported by the specification at, for instance, page 12, lines 8-9.

Claim 33 is supported by originally filed claim 33.

Claim 36 and 37 have been amended to correct antecedent basis of the term "amount."

The amendment to claims 36 and 38 to recite "secreted" is supported throughout the specification.

It is applicant's position that the amendments to the claims do not narrow the scope of the claims.

New claim 41 is supported by the specification at, for instance, page 12, lines 8-9, and by originally filed claim 29.

New claim 42 is supported by the specification at, for instance, page 12, lines 8-9, and by originally filed claim 33.

Examiner interview

The Examiner is thanked for the courtesies extended to the undersigned during the interview of March 26, 2002, where the rejections under §112, first paragraph and second paragraph, and the art based rejections were discussed.

The 35 U.S.C. §112, First Paragraph, Rejection

Claims 1-40 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, it was stated that "[s]ince the microorganisms are required and recited in each of the claims, it is essential to the whole invention as recited in those claims . . . . [and] must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public." The Action further states that the "specification does not disclose a repeatable process to obtain the microorganism and it is not apparent if the microorganism is readily available to the public." Claims 1-8 have been deleted without prejudice. This rejection is respectfully traversed.

Claims 1-7 have been canceled without prejudice. Applicant is presently preparing to deposit the strain referenced in claim 8, strain 10A. After strain 10A is deposited, the specification will be amended to comply with 37 C.F.R. §1.809(d).

Pending claims 8-15 and 20-42 do not explicitly recite the strains that are recited in claims 1-8, and are not limited to those strains. Further, it is applicant's position that a deposit is not needed under the circumstances, as bifidobacteria that secrete a siderophore can be isolated without undue experimentation. The specification discloses at Example 1 how *Bifidobacterium* strains were isolated. Fecal samples were obtained from human volunteers, the samples homogenized, plated and incubated under anaerobic conditions. The authenticity of individual colonies was verified by assessing the activity of a diagnostic enzyme for bifidobateria, and speciated using molecular analysis of the 16s rRNA or the *recA* gene. The specification further discloses at Example 2 the method used for detecting siderophore production by bifidobacteria. Individual *Bifidobacterium* strains were grown on nitrocellulose filters present on an agar plate containing an iron chelator, the filter removed after growth of the *Bifidobacterium*, and an indicator strain applied to the agar plate. The inhibition of growth of the indicator strains around the area on which the filter containing the bifidobacteria had been incubated indicated that the

Bifidobacterium produced a diffusible compound that inhibited growth of the indicator strains, and the inhibition by the compound was due to iron competition.

Each of these methods are routine and can be performed by a person of skill in the art without undue experimentation, thus, a deposit is not needed under the circumstances, as bifidobacteria that secrete a siderophore can be easily isolated without undue experimentation. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of the pending claims under 35 U.S.C. §112, first paragraph.

The 35 U.S.C. §112, Second Paragraph, Rejection

Claims 1-40 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These rejections are respectfully traversed.

Claims 9-12 were rejected as "vague and indefinite for 'a microbe' ." In claim 9, the phrase "measuring the presence of the microbe in the gastrointestinal tract" has been amended to recite "measuring the presence of a microbe that was present in the gastrointestinal tract of the animal prior to administration . . . ." It is respectfully submitted that a person of ordinary skill would recognize that these terms define the metes and bounds of the claims.

Independent claims 20 and dependent claims 21-26 were rejected as "vague and indefinite for whether or not the secretion of siderophore or Bifidobacterium which secretes is being measured . . . ." Claim 20 recites "measuring the presence of the *Bifidobacterium* in the gastrointestinal tract . . . ." Thus, claim 20 clearly states that the presence of the *Bifidobacterium* is measured. Accordingly, it is respectfully submitted that a person of ordinary skill would recognize that these terms define the metes and bounds of the claims.

The Action also states that independent claims 20 and dependent claims 21-26 were "rendered vague and indefinite for . . . whether there is any significant correlation between the two for the method of establishing the flora." The disclosure states there is a correlation. "It has been found that some strains of bifidobacteria isolated from the human intestine secrete compounds that prevent the acquisition of iron by microbes. The presence of these compounds

inhibits the *in vitro* growth of microbes. . . . Bifidobacteria secreting these compounds will inhibit the growth of other microbes in the gastrointestinal tract, especially the large intestine, of animals." Specification, page 5, line 28 through page 6, line 3. The specification also discloses at Example 2 evidence that the presence of a siderophore inhibits the *in vitro* growth of microbes.

Claim 27 was rejected as "vague and indefinite for failing to set forth clear and distinct process steps." Claim 27 clearly recites the process step of "adding to the food a *Bifidobacterium* that secretes a siderophore." Thus, claim 27 particularly points out and distinctly defines the metes and bounds of the claim.

Claim 28 was rejected as vague as indefinite for failing to clarify the comparison step. In claim 28, the phrase "detecting the presence of aberrant crypt foci in the colon of the animal, where a lower number of aberrant crypt foci relative to an animal not administered the *Bifidobacterium* indicates a decrease in the risk of colon cancer" has been amended to recite "detecting the presence of aberrant crypt foci in the colon of the animal, where a lower number of aberrant crypt foci compared to an animal not administered the *Bifidobacterium* indicates a decrease in the risk of colon cancer." The term "aberrant crypt foci" in claim 28 was asserted to be vague. The term "aberrant crypt foci" is recognized as an index of colon cancer risk (specification, page 16, line 26-30), and is well known to the art. As evidence of this, the Examiner is requested to consider Pretlow et al. (J. Cell Biochem. Suppl., 16G, 55-62 (1992), copy enclosed with the Information Disclosure Statement submitted herewith) , which describes in detail the morphology of aberrant crypts, and the relationship between colon cancer and the presence of aberrant crypts in rodents and humans. Further, since aberrant crypt foci are considered an index of colon cancer risk, any decrease in the number of aberrant crypt foci is indicative of a decrease in the risk of colon cancer.

The amendment to claim 29 renders the rejection of claim 29 moot.

Claim 30 was rejected as "vague and indefinite since it is unclear whether the siderophore is produced extracellularly or intra cellularly since it is secreted should it not be

obtained extracellularly." In the interests of furthering prosecution, claim 30 has been amended to recite "obtaining a secreted siderophore."

The metes and bounds of claims 31 and 32 were considered "unclear since it is uncertain how sterilization is to be carried out." It is respectfully submitted that a person of ordinary skill would recognize that the term "sterilizing" defines the metes and bounds of the claims. The meaning of the term "sterilizing" is well known to a person of skill in the art. Even if this term caused the metes and bounds of the claims to not be readily recognizable to one of skill in the art, the meaning of the term is clear in view of the disclosure. The specification discloses at page 13, line 15-26, that the culture can be treated by exposure to conditions to kill the bifidobacteria present in the culture, and examples of conditions useful for sterilization include heat or ultraviolet radiation.

With respect to the rejection of claim 32 that "removing all water is unclear as well," it is submitted that a person of ordinary skill would recognize that the recitation in claim 32 of "removing essentially all water from the culture" defines the metes and bounds of the claims. The meaning of "removing essentially all water from the culture" is well known to a person of ordinary skill. Moreover, the specification discloses at page 13, line 15-26, that the culture may be dried until essentially all moisture is removed and a powder containing the siderophore remains, and that methods for drying cultures are known to the art and include, for instance, spray drying, freeze drying, tunnel drying, vacuum drying, and air drying.

Claim 33 was rejected as "confusing and wordy and the phrase 'wherein the composition is sterile' should be deleted and the term 'sterile' inserted before 'composition' at line 1." In the interests of furthering prosecution, claim 33 has been amended to recite "a sterile composition." With respect to the assertion that "it is uncertain what else is in the composition beside the siderophore to make the claim a composition," the Examiner is respectfully requested to note that the claim recites "comprising," and thus is not limited by any other component that may be present in the composition.

Claims 34-39 were rejected as vague and indefinite as to how the siderophore is obtained. Claims 34 and 35, which are directed to "[a]n isolated siderophore . . ." are composition claims.

Claims 36-39 are directed to methods of using a siderophore or an isolated siderophore, and not directed to a product by process or a method of obtaining a siderophore. Thus, it is not necessary to describe how the siderophore is obtained.

Claim 40 was rejected as being vague and indefinite for failing to set forth clear and distinct process steps for altering the expression of a siderophore. Claim 40 recites "the method comprising incubating under iron limited conditions a *Bifidobacterium* that does not secrete a siderophore, and selecting for a *Bifidobacterium* that replicates in the iron limited condition." Thus, claim 40 recites the two acts of "incubating" and "selecting." It is respectfully submitted that a person of ordinary skill would recognize that "incubating" and "selecting" set forth clear and distinct process steps. Even if this term caused the metes and bounds of the claims to not be readily recognizable to one of skill in the art, the meaning of the term is clear in view of the disclosure. The specification discloses that after extensive *in vitro* culture, bifidobacteria can lose the ability to express a siderophore, and the ability to express a siderophore can be selected for by incubating on medium containing low levels of free iron a *Bifidobacterium* that does not express a siderophore (see specification at, for instance, page 18, lines 10-21).

The Examiner is requested to reconsider and withdraw the rejections of claims 1-40 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The 35 U.S.C. §§ 102(b) and 103(a) Rejections

Claims 1-9, 12-15, 20, 22-27, 29, 33-34, and 38-39 were rejected under 35 U.S.C. §102(b) as being anticipated by Mutai et al., and claims 16, 18-19, and 28 were rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, §103(a) as obvious over Rambaud et al. These rejections are respectfully traversed.

The invention of Mutai et al. is based on a "new strain of bifidobacteria, and relates to a method for producing a fermented milk product, characterized by cultivating this new strain of bifidobacteria in a milk medium such as whole milk, skim milk or reconstituted milk." Mutai et al., col. 1, lines 61-66. Mutai et al. further discloses that the cultivated product is desirable as

infant food of as an additive to infant food. Rambaud et al. is a review that pertains to dairy products and intestinal flora. Rambaud et al. disclose that intestinal bacteria fermenting lactose are "able to promote small intestinal lactose absorption in lactase deficient-sujects [sic] and modify the colonic flora echosystem [sic] in a way which could be beneficial to the host." Rambaud et al., page 397. Neither cited document teaches or suggests a *Bifidobacterium* that secretes a siderophore (claims 9, 16, 20, and 27-29) or a siderophore obtained from a *Bifidobacterium* (claims 33-34).

It is Applicant's position that Rambaud et al. has been mischaracterized. The Action asserts at page 8 that Rambaud et al. "teaches . . . decreasing the risk of colon cancer via administering a Bifidobacterium." However, at page 396, col. 2, Rambaud et al. states "[t]he relevance of these data on prevention of colonic carcinoma remains to be proven." Applicant was unable to find any other teaching in Rambaud et al. regarding colon cancer. Thus, it is applicants' position that Rambaud et al. do not teach decreasing the risk of colon cancer via administering a *Bifidobacterium*. The Examiner is respectfully requested to specify a passage within Rambaud et al. that discloses methods of decreasing the risk of colon cancer via administering a *Bifidobacterium*, or revise the characterization of the document.

The doctrine of inherency is used to support the contention that the cited documents disclose a siderophore produced by bifidobacteria. It is Applicant's position that the doctrine of inherency cannot be used to supplement the deficiencies of the cited documents. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art" (emphasis in original). M.P.E.P §2112. No basis in fact and no technical reasoning supporting the assertion of inherency is provided in the Action; only conclusory statements are provided. Thus, the Office has not made the initial showing required to rely upon the theory of inherency.

Further, the Examiner is requested to note that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" (emphasis in original). M.P.E.P §2112. "To establish inherency,

the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " M.P.E.P §2112.

The Examiner is respectfully requested to consider the following as evidence that the allegedly inherent characteristic does not necessarily flow from the teachings of the applied prior art. To begin with, the present application discloses that prior to the present invention, Bezkorovainy (In: Biochemistry and Physiology of Bifidobacteria, Bezkorovainy et al., (eds.), CRC Press, pp. 147-176 (1989)) investigated the ability of bifidobacteria to secrete a siderophore, and it was concluded that bifidobacteria did not (specification, page 5, lines 3-6, and lines 19-22). In particular, the Examiner is requested to note that Bezkorovainy teaches that "[i]ron transport in bifidobacteria does not involve the participation of siderophores" (page 174 of Bezkorovainy). Thus, a skilled person would not recognize that the bifidobacteria of the cited documents would necessarily secrete a siderophore. Secondly, the present application discloses in Examples 1 and 2 the isolation of bifidobacteria and detection of siderophore production by the bifidobacteria. Of the 29 strains isolated, 8 were found to produce a diffusible compound that was preferentially produced during incubation in low iron conditions and inhibited the growth of indicator strains. This observation that 8 of 29 strains produced the siderophore indicates that the ability to produce a siderophore is not necessarily present in all bifidobacteria.

Even if the strain disclosed in Mutai et al. and Rambaud et al. did produce a siderphore, such a property would be inherent only if there is at least a reasonable likelihood that one of skill in the art could have discovered or recognized that property without specific guidance. The subject matter relied upon must be disclosed in a manner to place it in possession of the public. See, e.g., Akzo N.V. v. United States Int'l Trade Comm'n., 1 USPA2d 1241 (Fed. Cir 1986).

The Examiner is requested to reconsider and withdraw the rejection of claims 1-9, 12-15, 20, 22-27, 29, 33-34, and 38-39 under 35 U.S.C. §102(b) in view of Mutai et al., and claims 16, 18-19, and 28 under 35 U.S.C. §102(b) or, in the alternative, §103(a) in view of Rambaud et al.

Summary

It is respectfully submitted that the pending claims 9-42 are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for

Daniel J. O'Sullivan

By
Mueting, Raasch & Gebhardt, P.A.
P.O. Box 581415
Minneapolis, MN 55458-1415
Phone: (612) 305-1220
Facsimile: (612) 305-1228
Customer Number 26813

26813

PATENT TRADEMARK OFFICE

April 11, 2002
Date

By: David L. Provence

Attorney Name: David L. Provence
Reg. No.: 43,022
Direct Dial: (612)305-1005

CERTIFICATE UNDER 37 CFR §1.10:
"Express Mail" mailing label number: EL888274777US Date of Deposit: April 11, 2002
The undersigned hereby certifies that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR §1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

By: Sue Dombroske
Name: Sue Dombroske

APPENDIX A - SPECIFICATION/CLAIM AMENDMENTS INCLUDING NOTATIONS TO INDICATE CHANGES MADE
Serial No.: 09/884,894
Docket No.: 110.01290101

Amendments to the following are indicated by underlining what has been added and bracketing what has been deleted. Additionally, all amendments have been shaded.

In the Claims

For convenience, all pending claims are shown below.

8. (Amended) An isolated *Bifidobacterium* having **all the identifying** [**the**] characteristics of strain 10A.

9. (Amended) A method for inhibiting the replication of a microbe in the gastrointestinal tract of an animal, comprising administering to an animal a *Bifidobacterium* that secretes a siderophore, and measuring the presence of **a** [**the**] microbe **that was present** in the gastrointestinal tract **of the animal prior to administration**, where a decrease in the presence of the microbe in the animal after administration of the *Bifidobacterium* indicates inhibition of the replication of the microbe.

10. The method of claim 9 further comprising growing the *Bifidobacterium* under iron limited conditions before administration.

11. The method of claim 10 wherein growing the *Bifidobacterium* under iron limited conditions comprises growth in the presence of an iron chelator.

12. The method of claim 9 wherein the animal is a human.

13. The method of claim 9 wherein the microbe is a prokaryotic microbe.

14. The method of claim 13 wherein the prokaryotic microbe is selected from the group consisting of *E. coli*, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Clostridium difficile*, and *Clostridium perfringens*.

15. The method of claim 9 wherein the gastrointestinal tract is the large intestine.

20. A method for establishing a *Bifidobacterium* flora in the gastrointestinal tract of an animal comprising administering to an animal a *Bifidobacterium* that secretes a siderophore, and measuring the presence of the *Bifidobacterium* in the gastrointestinal tract of the animal after administration.

21. The method of claim 20 further comprising growing the *Bifidobacterium* under iron limited conditions before administration.

22. The method of claim 20 wherein the gastrointestinal tract is the large intestine.

23. The method of claim 20 wherein the animal is a human.

24. The method of claim 23 wherein the human is an infant selected from the group consisting of an immature infant, a premature infant, and a mature infant.

25. The method of claim 23 wherein the administration occurs after the human has undergone antibiotic therapy.

26. The method of claim 23 wherein the administration occurs after the human has undergone chemotherapy.

27. A method for preventing the replication of microbes in a food, the method comprising adding to the food a *Bifidobacterium* that secretes siderophore.

28. (Amended) A method for decreasing the risk of colon cancer comprising administering to an animal a *Bifidobacterium* that secretes a siderophore, and detecting the presence of aberrant crypt foci in the colon of the animal, where a lower number of aberrant crypt foci **compared** [**relative**] to an animal not administered the *Bifidobacterium* indicates a decrease in the risk of colon cancer.

29. (Amended) A composition [**for inhibiting the replication of a microbe in the gastrointestinal tract of an animal, the composition**] comprising a *Bifidobacterium* that secretes siderophore.

30. (Amended) A method for obtaining a **secreted** siderophore from a *Bifidobacterium*, the method comprising incubating a *Bifidobacterium* under iron limited conditions, and isolating the siderophore.

31. A method for preparing a siderophore, the method comprising incubating a *Bifidobacterium* under iron limited conditions, and sterilizing the culture.

32. The method of claim 31 wherein the culture is sterilized by removing essentially all water from the culture.

33. (Amended) A **sterile** composition comprising a siderophore obtained from a *Bifidobacterium* [**, wherein the composition is sterile**].

34. An isolated siderophore obtained from a *Bifidobacterium*.

35. An isolated siderophore that binds Fe2+, the siderophore obtained from a *Bifidobacterium*.

36. (Amended) A method for decreasing an [the] amount of free iron in a composition, the method comprising adding to a composition a secreted siderophore obtained from a *Bifidobacterium*.

37. (Amended) A method for decreasing an [the] amount of free iron in a composition, the method comprising adding to a composition an isolated siderophore obtained from a *Bifidobacterium*.

38. (Amended) A method for inhibiting the replication of a microbe in a composition, the method comprising adding to a composition a secreted siderophore obtained from a *Bifidobacterium*.

39. A method for inhibiting the replication of a microbe in a composition, the method comprising adding to a composition an isolated siderophore obtained from a *Bifidobacterium*.

40. A method for altering the expression of a siderophore in a *Bifidobacterium*, the method comprising incubating under iron limited conditions a *Bifidobacterium* that does not secrete a siderophore, and selecting for a *Bifidobacterium* that replicates in the iron limited condition.

41. (New) A composition consisting essentially of a *Bifidobacterium* that secretes siderophore.

42. (New) A sterile composition consisting essentially of a siderophore obtained from a *Bifidobacterium*.